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Diagnosis of Fanconi Anemia in Patients Without Congenital Malformations: An International Fanconi Anemia Registry Study

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Data were analyzed from 419 Fanconi anemia (FA) patients enrolled in the American Registry of the International Fanconi Anemia Registry (IFAR) to determine whether Fanconi anemia (FA) patients without major congenital malformations (CM) have distinguishing characteristics that can lead to an earlier diagnosis. These included 377 patients reported by physicians to the IFAR and 42 patients examined by us. The number of FA patients in each group without CM was 128 and 16, respectively; one third of all patients lacked CM. We found that height, weight, and head circumference were ≤5th centile in 26.6%, 18.0%, and 8.6% of FA patients without CM referred to the IFAR, and in 43.8%, 25.0%, and 43.8% of FA patients without CM examined by us. Minor anomalies were reported in 9.4% of FA patients without CM referred to the IFAR and 100% of FA patients without CM examined by us. Most FA patients without CM have alterations in growth parameters, skin pigmentation abnormalities, or microphthalmia. Increased awareness of the complete spectrum of FA by clinicians will enable an earlier diagnosis to be made. Am. J. Med. Genet. 68:58–61, 1997

KEY WORDS: Fanconi anemia; minor congenital anomalies; microphthalmia; short stature; skin pigmentation abnormalities

INTRODUCTION

Since Fanconi's first description [1927] of three brothers between the age of 5 and 7 years with pancytopenia and birth defects, the spectrum of phenotypic findings in Fanconi anemia (FA) has been greatly expanded [Young and Alter, 1994]. Patients may be severely affected, with multiple congenital anomalies, or may have a mild phenotype, with no malformations. Phenotypic variability makes clinical diagnosis of FA difficult; the distinguishing characteristic is a cellular hypersensitivity to DNA cross-linking agents such as diepoxybutane (DEB), providing a unique marker for the FA genotype [Auerbach et al., 1981, 1989; Auerbach, 1993]. In a survey of the clinical findings obtained from the International Fanconi Anemia Registry (IFAR), we described a variety of gastrointestinal, central nervous system, and skeletal malformations in FA patients [Giampietro et al., 1993]. We reported that most FA patients with congenital malformations (CM) are not diagnosed until after the onset of hematologic abnormalities and postulated that delayed diagnosis could be due to lack of physician awareness of the phenotypic spectrum of FA.

In this study we address the issue of diagnosis of FA among patients without CM. Approximately one third of FA patients enrolled in the IFAR do not manifest CM; the diagnosis of FA is made only after they present with clinical symptoms of hematologic dysfunction. The mean time of diagnosis in this group is considerably later than for those FA patients with CM. Our analysis of the IFAR data indicates that most FA patients without CM have alterations in growth parameters, skin pigmentation abnormalities, and/or microphthalmia. We also describe minor anomalies found in FA. An increased awareness of these traits by the clinician could result in an earlier diagnosis of FA among patients without CM.

METHODS

The IFAR was established at The Rockefeller University in 1982 to collect clinical and genetic information from a large number of FA patients. The primary source of case material for the IFAR is voluntary physician reporting. Once a potential case is identified, an

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IFAR questionnaire form is completed by the referring physician and copies of laboratory reports and other patient records are obtained with the consent of the patient or guardian. Diagnosis of FA is confirmed by study of chromosomal breakage induced by DEB or other cross-linking agents in peripheral blood lymphocytes.

Clinical information from a total of 419 patients enrolled in the IFAR was analyzed. These included 377 patients reported to the IFAR, 128 of whom reportedly lacked CM and 42 patients examined by us, 16 of whom lacked CM. Minor anomalies are defined as unusual morphologic traits that are of no serious medical or cosmetic consequence to the patient. They can be found in the normal population or as parts of multiple congenital anomaly syndromes [Jones, 1991]. Mild malformations represent defects in organogenesis of a less severe nature [Opitz, 1985].

RESULTS

One third of FA patients enrolled in the IFAR did not have CM. A significant percentage of FA patients without CM were reported with height, weight or head circumference ≤5th centile (Table I). Minor anomalies and mild malformations reported among FA patients are listed in Table II; included in Table II are the percentages of FA patients with specific minor anomalies as reported by physicians on IFAR questionnaire forms as well as abnormalities detected by us on examination of patients. Among the 144 patients without CM, 28 (19.4%) were identified with minor anomalies, excluding skin pigmentation abnormalities and microphthalmia. Twelve of these patients were in the group of one hundred twenty-eight individuals reported to the IFAR as lacking in CM, while sixteen were in the group examined by us. Sixty-eight percent of FA patients without CM had height, weight, or head circumference ≤5%, skin pigmentation abnormalities, or microphthalmia; 64.1% of patients reported to the IFAR were found to have at least one of these traits, while 100% of patients examined by us had at least one. Even if skin pigmentation abnormalities are excluded, 75% of patients without CM examined at RU were found to have height, weight, or head circumference ≤5% or microphthalmia.

DISCUSSION

The IFAR data were analyzed in order to determine whether FA patients without CM have clinical signs that can lead to an earlier diagnosis. Since these findings are subtle and might be overlooked by physicians not fully aware of the complete spectrum of the FA phenotype, patients were divided into those only examined elsewhere and those examined by us. Short stature, skin pigmentation abnormalities, and microphthalmia were commonly found in patients lacking CM; 100% of FA patients without CM examined by us had at least one of these traits. However, a significantly lower proportion (64.1%) of patients examined elsewhere were reported to have one of these anomalies, indicating that they are frequently overlooked. Growth parameters were frequently not reported on IFAR questionnaires; for example, of the 128 patients without CM referred to the IFAR, head circumference was only reported for 15 patients.

In addition, we report a wide range of minor anomalies, thus expanding the phenotypic spectrum of FA. Again, these minor anomalies were detected with a much higher frequency among the population of FA patients examined by us as compared to the entire IFAR, thus emphasizing the need for clinicians to document the presence of minor anomalies in patients and to consider a diagnosis of FA in patients presenting with these traits. It is noteworthy that many FA patients have distinctive facial characteristics including microphthalmia and small facial size. Recognition of FA facial anomalies could lead to an earlier diagnosis of FA in some patients.

In many instances a complete blood count with differential is performed as a screening procedure in patients presenting with short stature and/or failure to thrive. The initial hematologic findings in FA include macrocytosis and decreased platelet count; these may be detected considerably earlier than the time of onset of clinical hematologic manifestations [Butturini et al., 1994]. If an alteration in either of these parameters is present, DEB testing should be performed.

A delay in diagnosis of FA can have serious consequences for patients and their families. An earlier diagnosis of FA would provide more time to explore different treatment options, including bone marrow transplantation from an HLA compatible donor. Although an HLA-identical sib is the preferred donor [Gluckman et al., 1989], it is sometimes necessary to use a matched unrelated donor [Gluckman et al., 1995]. Diagnosis before the onset of severe hematologic disease would provide more time to find a suitable donor for transplant. In addition, because FA is an autosomal

TABLE I. Growth Parameters Among FA Patients

	All FA patients		FA patients without CM	
Centile	Reported to IFAR (N = 377) % (n)	Examined at RU (N = 42) % (n)	Reported to IFAR (N = 128) % (n)	Examined at RU (N = 16) % (n)
Height ≤5	39.8 (150)	59.5 (25)	26.6 (34)	43.8 (7)
Weight ≤5	33.4 (126)	45.2 (19)	18.0 (23)	25.0 (4)
Head circumference ≤5	23.6 (89)	59.5 (25)	8.6 (11)	43.8 (7)

TABLE II. Minor Anomalies and Mild Malformations Among FA Patients

	All FA patients		FA patients without CM	
	Reported to IFAR (N = 377) % (n)	Examined at RU (N = 42) % (n)	Reported to IFAR (N = 128) % (n)	Examined at RU (N = 16) % (n)
Skin pigmentation[a]	63.7 (240)	83.3 (35)	55.5 (71)	100.0 (16)
Eye[b]	43.5 (164)	83.3 (35)	20.3 (26)	75.0 (12)
Nose[c]	0.8 (3)	35.7 (15)	2.3 (3)	37.5 (6)
Minor ear anomalies	10.3 (39)	38.1 (16)	3.9 (5)	18.8 (3)
Oral cavity[d]	1.9 (7)	33.3 (14)	0.8 (1)	18.8 (3)
Face[e]	0.8 (3)	31.0 (13)	0.8 (1)	18.8 (3)
Neck[f]	0.5 (2)	2.4 (1)	1.6 (2)	6.2 (1)
Hand[g]	11.9 (45)	47.6 (20)	7.0 (9)	56.2 (9)
Foot[h]	9.5 (36)	71.4 (30)	5.5 (7)	56.2 (9)
Prominent forehead	0.5 (2)	7.1 (3)	1.6 (2)	12.5 (2)
Other[i]	0.8 (3)	14.3 (6)	0 (0)	18.8 (3)

[a] Café-au-lait spots, hyperpigmentation, hypopigmentation.
[b] Short palpebral fissures (microphthalmia), almond shaped palpebral fissures, hypertelorism, hypotelorism, ptosis, and epicanthal folds.
[c] Flattened nasal bridge, and nasal pit.
[d] Arched palate, geographic tongue, and thin upper lip.
[e] Triangular face, facial asymmetry, and facial flattening.
[f] Webbing of neck, and low hairline.
[g] Thenar hypoplasia, clinodactyly of fifth digit, syndactyly of fingers, hyperextensible thumbs, arachnodactyly, and contractures.
[h] Syndactyly of toes, wide space between 1st and 2nd toe, pes planus, and hypoplastic toenails.
[i] Sacral dimple, frontal hair upsweep, chest asymmetry, and pectus excavatum.

recessive disorder with a recurrence risk of 25%, parents need to be informed of their reproductive risks and have an opportunity to consider their reproductive options.

FA is genetically heterogeneous, with at least five complementation groups identified by somatic cell hybrid studies [Strathdee et al., 1992a; Joenje et al., 1995]; however, the full extent of genetic heterogeneity remains to be determined. The gene *FAC* for complementation group C (FA-C) has been cloned [Strathdee et al., 1992b] and maps to 9q22.3 [Strathdee et al., 1992a]. The function of the *FAC* gene product is still unknown. Approximately 15% of FA patients have mutations in *FAC*; mutation analysis shows a correlation between genetic and clinical findings in persons with abnormalities in this gene [Verlander et al., 1994, 1995]. The two most common mutations in *FAC* are IVS4 +4 A $\rightarrow$ T and 322delG; all IVS4 patients exhibited multiple CM, while 322delG patients usually did not manifest CM. Non-FA-C patients also include individuals with and without CM.

Thus, most FA patients who lack CM have alterations in growth, skin pigmentation abnormalities, or microphthalmia. In addition, all FA patients without CM examined by us have other minor anomalies. An increased awareness of the complete spectrum of FA by clinicians will result in an earlier diagnosis of the syndrome.

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